LETTERS TO THE EDITOR

Very early onset Alzheimer's disease with spastic paraparesis associated with a novel presenilin 1 mutation (Phe237Ile)

Mutations in the presenilin 1 (PS1) gene (PS1) are responsible for 30%–40% of early onset familial Alzheimer's disease and over 60 mutations have been found so far. There are phenotypic variations among mutations on PS1. Three PS1 mutations, deletion of exon 9 with and without splice acceptor site mutation, and Arg278Thr have been reported to be associated with Alzheimer's disease with spastic paraparesis.[1 2] We report clinical and genetic features of a man who developed very early onset Alzheimer's disease with spastic paraparesis, which was associated with a novel mutation of PS1, Phe237Ile.

A 35 year old Japanese man had graduated from a national university and had worked as a psychiatric counsellor for a local clinic. His first neurological symptom was gait disturbance at the age of 31. At the age of 32, mild memory impairment and decreased mental activity were noted. His neurological deficits progressed gradually. On neurological evaluation at the age of 33, diffuse hyperreflexia, ataxia in all limbs, bilateral Babinski's sign, and dementia (total IQ on the WAIS-R of 75) were noted. He gave up his job at this time. At the age 34, he could not live alone because of memory deficit and cognitive dysfunction (total IQ on the WAIS-R of 59). At the age of 35, he became bedridden due to deterioration of spastic paraparesis, and presented with partial or generalised seizures a few times. His parents (66 and 63 years old) and sibling (27 years old) had no neurological deficits. There was no similar disease in other members of his family. On admission, he was alert and oriented for place, but not for time. He had severe difficulties in immediate and delayed recall of presented materials. He could not answer his name and occupation, but could sometimes follow three step commands. He spoke only two word sentences and could not write any words. He also had difficulties in speech comprehension. His score on the mini mental state examination was 5. Cranial nerves were normal except for dysarthria. Deep tendon reflexes were hyperreactive and plantar responses were extensor bilaterally. Muscle tone was rigid and spastic in all limbs. He had neck dystonia. No apparent weakness was noted. He presented generalised bradykinesia. He had myoclonic involuntary movement in his face and arms. Sensation remained intact. There was no remarkable abnormality in coordination. He was incontinent of urine. The protein concentration in CSF was increased at 73 mg/l whereas the cell count was normal. The concentrations of neuron specific enolase (23.6 ng/ml) and tau protein (722 pg/ml) in CSF were increased. An EEG showed generalised slowing with background theta. Somatosensory evoked potential was normal. Brain MRI showed diffuse cerebral cortical atrophy. PET with 2-^{18}F-fluoro-2-deoxy-D-glucose as a ligand and a Tc-99m-ECD SPECT study demonstrated remarkable hypometabolism and hypoperfusion in the bilateral temporoparietal areas including the primary sensory and motor cortex, respectively.

Genomic DNA was extracted from blood. The whole coding exons of PS1 and prion protein gene (PRNP), exon 16 and 17 of the amyloid β protein precursor gene (APP), and splice acceptor site of intron 8 were amplified using a polymerase chain reaction (PCR) with primers previously described.[3–5] Sequencing of both the sense and complementary strand of the PCR product were performed by ABI PRISM model 310 using the ABI PRISM BigDye™ terminator cycle sequencing ready reaction kit (Perkin-Elmer, CA, USA). The novel mutation Phe237Ile in PS1 was confirmed by restriction fragment length polymorphism. The PCR product was digested with Hph I (Biolabs) and was resolved in 1.5% agarose gel. A normal allele was characterised by the single fragment of 369 bp and a mutated allele by two fragments of 248 and 121 bp. We also searched for this mutation in 197 Japanese patients from a necropsy series at a geriatric hospital in Tokyo (73 non-demented controls without CNS disorder, 59 sporadic patients with Alzheimer's disease, and 65 disease controls with various CNS disorders).[6] The possibility that large segments of PS1 were spliced out was also examined. RNA extracted from the blood was reverse transcribed and PCR was performed to produce cDNA from exon 3 to exon 12 of PS1 (sense primer: 5'-GTTACC TGCACCGTTGTCCTACT-3', antisense primer: 5'-GGAGATTGGAAGAGCTGGC AATG-3').[7] The PCR product was analyzed

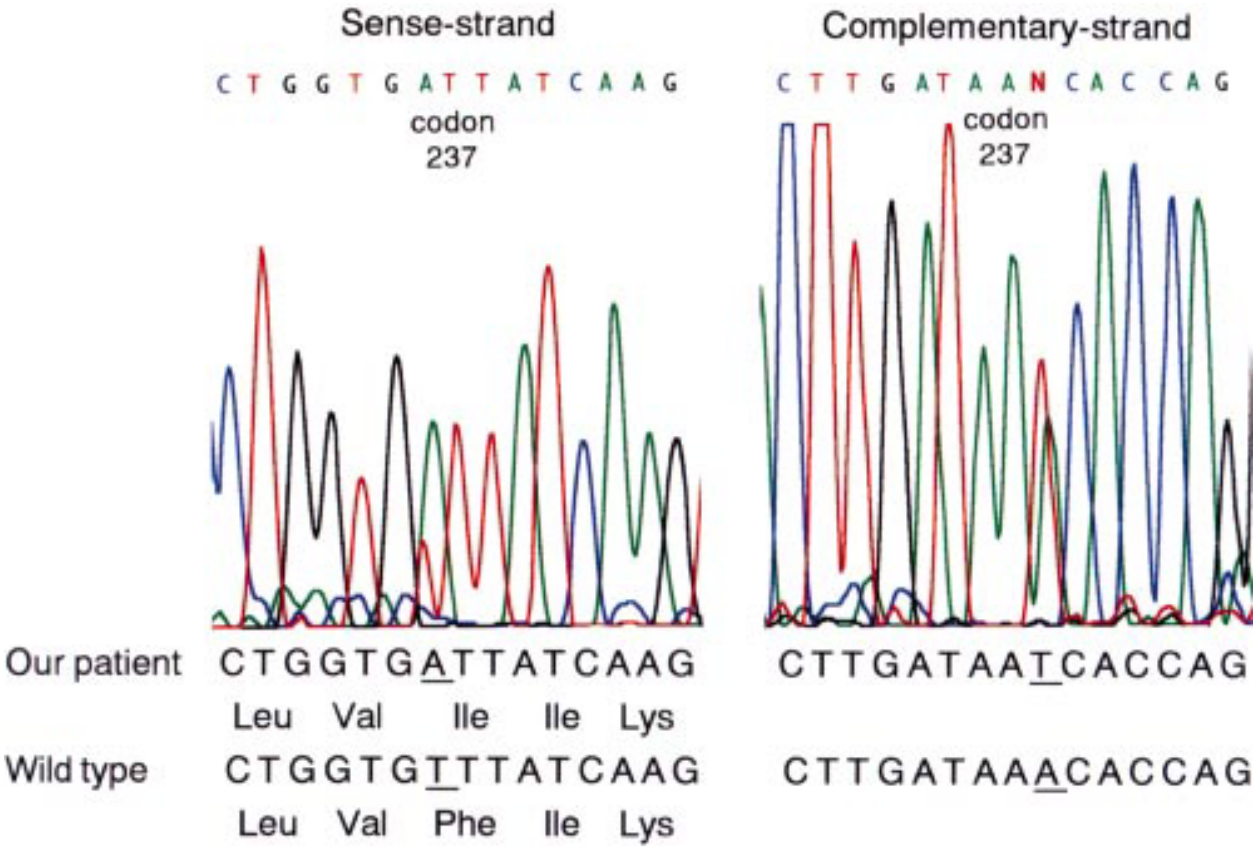

Figure 1 DNA sequence of exon 7 of PS1 of our patient and wild type. The patient has T to A transition at the first position of codon 237 leading to the Phe237Ile mutation.

in 1.5% agarose gel. The apolipoprotein E gene (ApoE) was also genotyped as described previously.[6] All analyses were confirmed by a repeat procedure. The remainder of the patient's family members did not consent to genetic examination.

Sequence analysis of PS1 disclosed a novel heterozygous T to A transition at the first position of codon 237 (fig 1). This mutation is predicted to result in the substitution of a phenylalanine for isoleucine (Phe237Ile). Restriction analysis confirmed the presence of a heterozygous mutation of Phe237Ile. There was no additional mutation in the whole coding exons of PS1 and PRNP, exon 16 and 17 of APP, or splice acceptor site of intron 8. Phe237Ile mutation was not found in 197 patients from the necropsy series. There was no deletion of the large segment of PS1 cDNA including exon 9, which was previously reported in familial Alzheimer's disease with spastic paraparesis.[2] The ApoE genotype of our patient was 3/3.

As there is no similar disease in his family and DNA samples from the remainder of the family members were not available, we cannot authenticate the relation between genetic abnormality and development of the disease. However, we suppose that the PS1 Phe237Ile is responsible for pathogenesis of our patient for five reasons.

Firstly, mutation in PS1 is the most popular genetic cause of familial Alzheimer's disease (FAD) and all mutations except Glu318Gly are responsible for early onset Alzheimer's disease.[8] Glu318Gly is a frequent polymorphism which is found in 3.3% of the general population.[8] To exclude the possibility that Phe237Ile is a polymorphism in a Japanese population, we screened for the presence of Phe237Ile in 197 patients from a necropsy series including non-demented controls and patients with sporadic Alzheimer's disease. The same mutation was not found in this population, suggesting that Phe237Ile is a rare mutation associated with FAD.

Secondly, two mutations in the transmembrane V domain produce very early onset Alzheimer's disease. The patients with Leu235Pro developed Alzheimer's disease at ages 29–35 and the patients with Met233Thr in their early 30s.[1 9] Our patient also manifested his first neurological symptom at the age of 31.

Thirdly, three mutations of PS1, loss of exon 9 with or without mutation splice acceptor site mutation, and Arg278Thr are associated with Alzheimer's disease with spastic paraparesis.[1 2]

Forthly, codon 237 is well preserved in the related proteins such as the human PS1, human PS2, mouse PS1, and *Caenorhabditis elegans* Sel-12 protein. These data indicate that this region is important for the function of PS1 and mutation in codon 237 is certainly pathogenic.

Fifthly, PET examination showed hypometabolism in the temporoparietal lobes, which is a typical metabolic deficit of Alzheimer's disease. The similar pattern of hypometabolism was reported in the patients with variant Alzheimer's disease with spastic paraparesis.[10] The result of the SPECT study was also compatible with diagnosis of Alzheimer's disease.

As the combination of five reasons as mentioned above is hardly explained by chance, we suppose that our clinical and genetic findings would be sufficient to diagnose our patient as having Alzheimer's disease with spastic paraparesis associated with the PS1 Phe237Ile mutation. We should examine genomic DNA and mRNA of PS1 from the patient with dementia and spastic paresis, even if it is an apparent sporadic case. Further collection of similar cases would establish clinical characteristics of Alzheimer's disease associated with the PS1 Phe237Ile mutation.

The study was supported in part by a Health Science Research Grant (to MY) from the Ministry of Health and Welfare, Japan and Grants in Aid for Scientific Research (to HM and MY) from the Ministry of Education, Science, Sports, and Culture, Japan.

N SODEYAMA
T IWATA
K ISHIKAWA
H MIZUSAWA
Department of Neurology and Neurological Science, Tokyo Medical and Dental University Graduate School of Medicine, Yushima 1–5–45, Bunkyo-ku, Tokyo 113–8519, Japan

M YAMADA
Department of Neurology, Kanazawa University School of Medicine, Kanazawa, Japan

Y ITOH
E OTOMO
Department of Internal Medicine, Yokufukai Geriatric Hospital, Tokyo, Japan

M MATSUSHITA
Department of Neuropathology, Tokyo Institute of Psychiatry, Tokyo, Japan

Y KOMATSUZAKI
Department of Internal Medicine, Hatsuishi Hospital, Chiba, Japan

Correspondence to: Dr N Sodeyama
n-sodeyama.nuro@tmd.ac.jp

1 Kwok JBJ, Taddei K, Hallupp M, *et al*. Two novel (M233T and R278T) presenilin-1 mutations in early-onset Alzheimer's disease pedigrees and preliminary evidence for association of presenilin-1 mutations with a novel phenotype. *Neuroreport* 1997;**8**:1537–42.
2 Crook R, Verkkoniemi A, Perez-Tur J, *et al*. A variant of Alzheimer's disease with spastic paraparesis and unusual plaques due to deletion of exon 9 of presenilin 1. *Nat Med* 1998;**4**: 452–5.
3 Hutton M, Busfield F, Wragg M, *et al*. Complete analysis of the presenilin 1 gene in early onset Alzheimer's disease. *Neuroreport* 1996;**7**:801–5.
4 Furukawa H, Kitamato T, Hashiguchi H, *et al*. Japanese case of Creutzfeldt-Jakob disease with a point mutation in the prion protein gene at codon 210. *J Neurol Sci* 1996;**141**:120–2.
5 Adroer R, Chartier-Harlin M-C, Crawford F, *et al*. Improved direct sequencing of Alzheimer's amyloid precursor protein (APP) exon 16 and 17. *Neurosci Lett* 1992;**141**:69–71.
6 Sodeyama N, Yamada M, Itoh Y, *et al*. α2-macroglobulin polymorphism is not associated with AD or AD-type neuropathology in the Japanese. *Neurology* 2000;**54**:443–6.
7 Perez-Tur J, Froelich S, Prihar G, *et al*. A mutation in Alzheimer's disease destroying a splice acceptor site in the presenilin-1 gene. *Neuroreport* 1995;**7**:297–301.
8 Dermaut B, Cruts M, Backhovens H, *et al*. Familial Creutzfeldt-Jakob disease in a patient carrying both a pesenilin 1 missense substitution and a prion protein gene insertion. *J Neurol* 2000;**247**:364–8.
9 Campion D, Brice A, Dumanchin C, *et al*. A novel presenilin 1 mutation resulting in familial Alzheimer's disease with an onset age of 29 years. *Neuroreport* 1996;**7**:1582–4.
10 Verkkoniemi A, Somer M, Rinne JO, *et al*. Variant Alzheimer's disease with spastic paraparesis: clinical characterization. *Neurology* 2000;**54**:1103–9.

Evaluation of CSF biomarkers for axonal and neuronal degeneration, gliosis, and β-amyloid metabolism in Alzheimer's disease

Although the accuracy rate of the clinical diagnosis of Alzheimer's disease is around 75%–90%, it is probably considerably lower early in the disease course, when symptoms are vague. Therefore, in view of potential future disease modifying compounds there is a great need for reliable diagnostic biochemical markers for Alzheimer's disease in CSF.

Such markers should reflect the central pathogenic processes of the disease—that is, the disturbance in the metabolism of β-amyloid (Aβ) with subsequent Aβ deposition in senile plaques, the hyperphosphorylation of tau protein with subsequent formation of neurofibrillary tangles, neuronal degeneration, and gliosis.

Two promising biomarkers are tau protein (reflecting neuronal and axonal degeneration) and Aβ42 (reflecting disturbances in Aβ metabolism and possibly Aβ deposition in senile plaques). The ability of the combination of CSF tau and CSF Aβ42 to differentiate Alzheimer's disease from normal aging and depression is high, about 85%, also early in the course of the disease.[1] Similarly, most degenerative neurological disorders have normal concentrations. However, the specificity against other dementias is not optimal.[1] Thus, there is a need for additional CSF biomarkers for Alzheimer's disease, to further increase the diagnostic accuracy.

We therefore examined whether the addition of other CSF biomarkers (two neuronal and two glial proteins) would add further to the diagnostic ability to identify Alzheimer's disease. The neuronal proteins were neurofilament protein light subunit (NFL), the major protein component of neurofilaments (probably reflecting degeneration of myelinated axons) and neuron specific enolase (NSE), a neuronal glycolytic enzyme (probably reflecting degeneration of neuronal cell bodies). The glial proteins were glial fibrillary acidic protein (GFAP), an astrocyte specific protein considered to be the major component of glial filaments in reactive astrocytes, and S-100β, a calcium binding protein also found in astrocytes (both reflecting gliosis).

From the longitudinal geriatric population study in Piteå, Sweden[2] we studied 35 patients with Alzheimer's disease, mean age 72.1 (SD 5.9) years, duration of disease of 48.9 (SD 32.0) months, and with MMSE scores of 23.5 (SD 4.7). The control group consisted of 19 subjects, mean age 71.2 (SD 7.3) years, without symptoms or signs of brain disorders, all with MMSE scores above 28.

The ethics committees at the universities of Umeå and Göteborg approved the study, conducted in accordance with the provisions of the Helsinki Declaration.

Analyses of CSF were performed using enzyme linked immunosorbent assays (ELISAs) as described previously in detail for total tau, Aβ42,[1] NFL,[3] GFAP,[4] and S-100β.[5] The NSE in CSF was determined using a commercial ELISA from AB Sangtec Medical, Bromma, Sweden.

The Mann-Whitney *U* test was used for group comparisons and the Pearson correlation coefficient for correlations. The dataset was also investigated by principal component analysis using the SIMCA-S software (Umetri AB, Umeå, Sweden), and by partial least squares with cross validation as a validation tool for multivariate correlations between CSF biomarkers and diagnosis.

When comparing CSF biomarkers between patients with Alzheimer's disease and controls (values given as means (SD)), there was a significant increase in CSF tau (634 (288) *v* 375 (171) pg/ml; $p<0.0001$), and in CSF NFL (615 (456) *v* 295 (194) pg/ml;

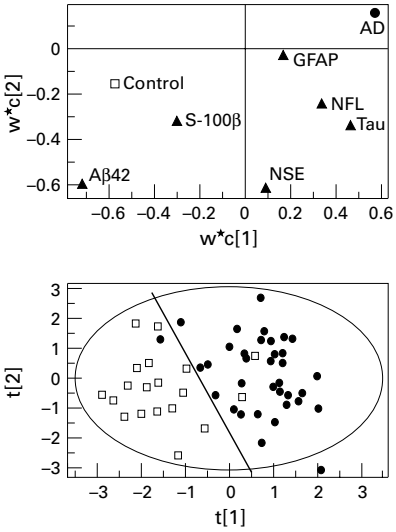

Figure 1 Top: CSF biomarker intercorrelation for principal components 1 and 2 from partial least squares-discriminant analysis. The discriminant regressor was Alzheimer's disease (filled circle) or healthy control (open square). Highest correlation was found for Aβ42 with Alzheimer's disease. Tau and NFL also correlated with Alzheimer's disease; however, including some structure not related to the disease (loading in principal component 2). Bottom: Interindividual scores of included study objects for principal components 1 and 2 from partial least squares-DA. The principal components were derived by a projection of assessed CSF protein concentrations (included protein assessment as in the figure above). Filled circles=Alzheimer's disease; open squares=healthy controls.

p=0.002). There was also a significant decrease in CSF Aβ42 in patients with Alzheimer's disease compared with controls (748 (297) *v* 1623 (429) pg/ml; p<0.0001) and a slight but significant decrease in CSF S-100β (1.8 (0.9) *v* 2.5 (0.9) µg/l; p=0.014). By contrast, there were no significant differences in CSF-NSE (7.4 (2.7) *v* 6.9 (2.1) µg/l; p=0.568) or CSF GFAP (860 (297) *v* 717 (250) ng/l; p=0.097).

The combination of CSF tau and CSF Aβ42 gave at best a sensitivity of 32/35 (91.4%) and a specificity of 17/19 (89.5%). A partial least squares analysis with all CSF biomarkers and clinical groups (Alzheimer's disease and controls), showed a relation between a diagnosis of Alzheimer's disease and high CSF tau, high CSF NFL, high CSF GFAP, and low CSF Aβ42 concentrations (fig 1). The NSE and S-100β in CSF showed no discriminative power so these additional biomarkers gave no further aid in the discrimination between Alzheimer's disease and controls. The sensitivity using all CSF biomarkers was 34/35 (97.1%) and the specificity was 17/19 (89.5%).

In agreement with previous findings, increased CSF tau and decreased CSF Aβ42[1] was found in Alzheimer's disease, resulting in a good sensitivity and specificity for discriminating Alzheimer's disease from controls. As the ability of these CSF biomarkers to discriminate Alzheimer's disease from other dementia disorders is less than optimal, we tested whether the combined analysis of additional biomarkers for axonal degeneration (CSF NFL), neuronal degeneration (CSF NSE), and gliosis (CSF GFAP and CSF S-100β) resulted in any further increase in the diagnostic sensitivity or specificity. However, there was only a marginal increase in sensitivity (from 91.4% to 97.1%) whereas the specificity was unchanged (89.5%). Therefor we conclude that these biomarkers have little additional value as diagnostic biochemical markers for Alzheimer's disease.

We hypothesise that other biomarkers more specifically related to Alzheimer's disease pathogenesis, such as hyperphosphorylated tau, synapse specific proteins (for example, rab3a, synaptotagmin), or APP isoforms (for example, α-secretase or β-secretase cleaved APP), may have a larger potential as CSF biomarkers for Alzheimer's disease.

This work was supported by grants from the Swedish Medical Research Council (grants 12103 and 11560); Alzheimerfonden, Lund, Sweden; Stiftelsen för Gamla Tjänarinnor, Stockholm, Sweden; Tore Nilssons Fond för Medicinsk Forskning, Stockholm, Sweden; Norrbottens Läns Landstings FoU Fond, Sweden; Svenska Läkaresällskapet, Stockholm, Sweden; and Åke Wibergs Stiftelse, Stockholm, Sweden. We are grateful to Mrs Christina Sjödin and Mrs. Maria Lindbjer for skillful technical assistance.

N ANDREASEN
Department of Rehabilitation, Piteå River Valley Hospital, PO Box 715, SE-941 28 Piteå, Sweden

J GOTTFRIES
Astra-Zeneca, Mölndal, Sweden

E VANMECHELEN
H VANDERSTICHELE
Innogenetics, Ghent, Belgium

P DAVIDSSON
K BLENNOW
Department of Clinical Neuroscience, Section of Experimental Neuroscience, University of Göteborg, Sahlgren's University Hospital, Mölndal, Sweden

L ROSENGREN
Department of Clinical Neuroscience, Section of Neurology, University of Göteborg, Sahlgren's University Hospital, Göteborg, Sweden

K BLENNOW
The Medical Research Council, Sweden

Correspondence to: Dr N Andreasen
niels.andreasen@nll.se

1 Andreasen N, Minthon L, Davidsson P, *et al*. Evaluation of CSF-tau and CSF-Aβ42 as diagnostic markers for Alzheimer's disease in clinical practice. *Arch Neurol* 2001;**58**:373–9.
2 Andreasen N, Blennow, Sjödin C, *et al*. Prevalence and incidence of clinically diagnosed memory impairments in a geographically defined general population in Sweden. The Piteå dementia project. *Neuroepidemiology* 1999;**18**:144–55.
3 Rosengren LE, Karlsson JE, Karlsson JO, *et al*. Patients with amyotrophic lateral sclerosis and other neurodegenerative diseases have increased levels of neurofilament protein in CSF. *J Neurochem* 1996;**67**:2013–8.
4 Rosengren LE, Wikkelsö C, Hagberg L. A sensitive ELISA for glial fibrillary acidic protein: application in CSF of adults. *J Neurosci Methods* 1994;**51**:197–204.
5 Aurell A, Rosengren LE, Wikkelsö C, *et al*. The S-100 protein in cerebrospinal fluid: a simple ELISA method. *J Neurol Sci* 1989;**89**:157–64.

Variant Creutzfeldt-Jakob disease is not associated with individual abilities to metabolise organophosphates

Since its identification as a distinct form of human prion disease, it has been demonstrated that vCJD is related to bovine spongiform encephalopathy (BSE),[1] thus providing evidence for transmission of the disease from cattle to humans. Despite widespread beef consumption, however, the number of cases of vCJD has been low and moreover, there is no history of unusual exposure to beef or its products among affected persons,[1] These findings may arise from a combination of factors, including the existence of environmental factors that may affect susceptibility, the long incubation period for vCJD, uneven exposure to infected beef, and variations in individual genetic susceptibility to the transmission process. Of the known genetic factors, it has been established that polymorphisms of codon 129 of the prion protein gene confer individual susceptibility to vCJD.[1] However, this polymorphism is common in the normal population, suggesting that other genes contribute to genetic susceptibility to vCJD.

This study aimed to establish whether polymorphisms in the paraoxonase (PON) family of genes are associated with incidence of vCJD and was based on the hypothesis that exposure to OPs, widely used as insecticides in the United Kingdom, was causally related to the BSE epidemic.[2] PON1 and PON2 have a major role in the detoxification of many organophosphate pesticides: PON1 allelic variants confer fast or slow abilities to detoxify these xenobiotics.[3] PON1 is also known to protect against accumulation of potentially harmful oxidised lipids: this scavenging role of PON1 has been used to provide a rationale for the association of both PON1 and PON2 polymorphic variants with predisposition to heart disease.[4]

The rationale for our study is also supported by the finding that, in cultured cells, the organophosphate pesticide phosmet, widely used at high doses in the United Kingdom to eradicate warble fly, upregulates cell surface levels of normal prion protein in human neuronal cells[5]; high levels of PrP expression are themselves known to be associated with increased ease of transmission of prion diseases.[1] Although it has been shown that vCJD does not seem to be associated with exposure to organophosphates present in head lice treatments,[6] our study aimed to establish whether persons affected by vCJD are more genetically susceptible to organophosphate exposure than the normal population.

Using the polymerase chain reaction and restriction analysis, we genotyped 26 patients with vCJD, 19 patients with sporadic CJD, and 10 neurological controls for both codon 54 and 192 of PON1 and codon 311 of PON2 polymorphisms.[3–4] In addition, we genotyped 93, 117, and 95 normal persons, respectively for codon 54 and 192 of PON1 and codon 311 of PON2 polymorphisms.

All patients were clinically diagnosed and neuropathologically confirmed. None of the patients with vCJD that we studied belonged to the cluster recently found in Leicestershire.[7]

Statistical analysis of the data was performed using the Pearson's χ^2 test ($p<0.05$).

The distribution of PON1 and PON2 genotypes and allele frequencies in patients and controls is shown in table 1. All genotype frequencies did not deviate significantly from the predicted Hardy-Weinberg equilibrium (data not shown). The frequencies of alleles L(Leu) and M(Met) at codon 54 of PON1 were respectively 0.672 and 0.328 in the control population (n=93), 0.654 and 0.346 in vCJD, 0.684 and 0.316 in sporadic CJD, and 0.700 and 0.300 in neurological controls. The frequencies for alleles A(Gln) and B(Arg) at codon 192 of PON1 were respectively 0.726 and 0.274 (n=117) in the controls, 0.731 and 0.269 in vCJD, 0.737 and 0.263 in sporadic CJD, and 0.700 and 0.300 in neurological controls. Finally, the frequencies for alleles S(Ser) and C(Cys) at codon 311 of PON 2 were respectively 0.774 and 0.226 in controls (n=95), 0.769 and 0.231 in vCJD, 0.763 and 0.237 in sporadic CJD, and

*Table 1 Distribution of PON1 and PON2 genotypes and allele frequencies in cases and controls**

	Controls	*Neurological controls*	*Sporadic CJD*	*Variant CJD*
PON1:				
Codon 54				
Genotype				
LL	38 (40.9)	4 (40)	7 (36.8)	8 (30.8)
LM	49 (52.7)	6 (60)	12 (63.2)	18 (69.2)
MM	6 (6.4)	—	—	—
n	93	10	19	26
Allele				
L(Leu)	0.672	0.700	0.684	0.654
M(Met)	0.328	0.300	0.316	0.346
Codon 192:				
Genotype				
AA	63 (53.8)	5 (50)	10 (52.6)	14 (53.8)
AB	44 (37.6)	4 (40)	8 (42.1)	10 (38.5)
BB	10 (8.5)	1 (10)	1 (5.3)	2 (7.7)
n	117	10	19	26
Allele				
A(Gln)	0.726	0.700	0.737	0.731
B(Arg)	0.274	0.300	0.263	0.269
PON2:				
Codon 311				
Genotype				
SS	57 (60)	5 (50)	12 (63.2)	15 (57.7)
CS	33 (34.7)	4 (40)	5 (26.3)	10 (38.5)
CC	5 (5.3)	1 (10)	2 (10.5)	1 (3.8)
n	95	10	19	26
Allele				
S(Ser)	0.774	0.700	0.763	0.769
C(Cys)	0.226	0.300	0.237	0.231

Values in parentheses are percentages. All data were analysed using Pearson's χ^2 test (significance taken as $p<0.05$). There were no significant differences between the cases and controls.

0.700 and 0.300 in neurological controls. There was no significant association between any of the PON polymorphisms studied and vCJD, sporadic CJD, or the other neurological disorders (table 1). Our data show that PON polymorphic variants are not associated with vCJD. These data, together with the data of Churchill *et al*,[6] indicate that exposure to organophosphates is unlikely to contribute to the incidence of vCJD.

We thank Dr Maureen Marks for statistical help and advice.

O GAROFALO
EH MCFARLANE
C IYEGBE
S A WHATLEY
I C CAMPBELL
Institute of Psychiatry, Department of Neuroscience, De Crespigny Park, King's College London, London SE5 8AF, UK

N KOPP
Hopital Neurologique, Lyon, France

R G WILL
National CJD Surveillance Unit, Edinburgh EH4 2XV, UK

Correspondence to: Professor I C Campbell
i.campbell@iop.kcl.ac.uk

1 Collinge J. Variant Creutzfeldt-Jakob disease. *Lancet* 1999;**354**:317–22.
2 Fishbein L. Transmissible spongiform encephalopathies, hypotheses and food safety: an overview. *Sci Total Environ* 1998;**217**:71–82.
3 Humbert R, Adler DA, Disteche CM, *et al*. The molecular basis of the human serum paraoxonase activity polymorphism. *Nat Genet* 1993;**3**: 73–6.
4 Sanghera DK, Aston CE, Saha N, *et al*. DNA polymorphisms in two paraoxonase genes (PON1 and PON2) are associated with the risk of coronary artery disease. *Am J Hum Genet* 1998;**62**:20–4.
5 Gordon I, Abdulla EM, Campbell IC, *et al*. Phosmet induces up-regulation of surface levels of the cellular prion protein. *Neuroreport* 1998;**9**:1391–5.
6 Churchill D, Churchill DJ, Will RG. Organophosphate exposure and variant Creutzfeldt-Jakob disease. *Lancet* 1999;**353**:1410.
7 Anonymous. Variant Creutzfeldt-Jakob disease in Leicestershire. *Commun Dis Rep CDR Wkly* 2000;**10**:257.

Monitoring an electroencephalogram for the safe application of therapeutic repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has come to be widely used to evaluate the CNS since the first report on the use of TMS in humans by Barker *et al*[1] in 1985. Depending on the frequency, intensity, and duration of stimulation, trains of repetitive TMS (rTMS) can transiently block or inhibit the function of a cortical region.It has been suggested that rTMS has therapeutic potential for the treatment of Parkinson's disease[2 3] and psychiatric disorders.[4] To apply rTMS as a clinical tool, an evaluation of the safety margins during the stimulation is required.

A 56 year old woman was admitted to Hokkaido University Medical Hospital on 6 October 1999 for treatment of involuntary movement of the trunk and lower limbs that had persisted for 8 years. In 1991, the patient had a spinal cord injury at thoracic and lumbar levels and a shearing fracture at the level of L1/L2. At that time, neurological examination disclosed paresis of the lower limbs, and the patient underwent a posterior fixation. Involuntary movement in her left thigh began a few months after the injury. In 1997, the involuntary movement became worse and had spread from the trunk to both limbs.

Examination using a surface EMG showed that the involuntary movement consisted of an elevation of the pelvis and a flexion and rotation of the trunk via the bilateral rectus abdominis, obliquus externus abdominis, and obliquus internus abdominis. Extension of the trunk also occurred during the involuntary movement via the bilateral quadratuus lumborum and iliocostalis lumborum. In addition, an involuntary contraction of bilateral gluteus maximus muscles was seen in the hip joints. The occurrence of the involuntary movement was irregular and was not precipitated by any obvious conditions.

The patient was able to perform voluntary movement via the bilateral rectus abdominis, obliquus externus abdominis, and obliquus internus abdominis muscles, but she was not able to perform voluntary movement using the hip flexors, which are under the contral of L2, and lower level muscles. An EEG, recorded at rest, and MRI of the brain showed no significant abnormalities. In addition, the patient had no history of seizure.

Treatment was by means of drugs (clonazepam and haloperidol), transcutaneous electrical nerve stimulation of the lower intercostal nerve, which innervates the obliquus externus abdominis, and a lumbar extradural nerve block at the level of T10–12. However, these treatments had no effect on the involuntary movement.

A trial study of rTMS was designed to investigate whether it could improve the involuntary movement of the trunk and lower limbs. The study was performed using a commercially available stimulator (MagStim 200) and a round coil (13 cm in diameter) according to the following protocol: 50 stimuli of 0.25-Hz rTMS at the intensity of 110% of the motor threshold were delivered to the right prefrontal cortex in the counterclockwise direction of the electrical current in the coil. In succession, 50 stimuli of 0.25-Hz rTMS at the intensity of 110% of the motor threshold were delivered to the left prefrontal cortex in the clockwise direction of the electrical current in the same coil. One session consisting of these 100 stimuli was delivered once a day and was repeated for 5 consecutive days.

The motor threshold was assessed by application of a single stimulation with interstimulus interval of more than 10 seconds to the presumed motor area[5] for activation of the contralateral abductor pollicis brevis muscle.[3 4] The directions of the electrical current of motor threshold measurement and rTMS of the ipsilateral prefrontal cortex were the same. This assessment was carried out an hour earlier than the first rTMS session. Motor threshold intensity was defined as the lowest stimulation intensity that induced five motor evoked potentials (MEPs) of 0.05 mV in peak to peak amplitude in 10 trials. Motor threshold intensities of the right and left abductor pollicis brevis muscles were 55% and 52% of the maximum stimulator output, respectively.

Left and right prefrontal cortex stimulations were defined as stimulations with the same coil centred over a point 5 cm anterior to the frontal scalp position for activation of the contralateral abductor pollicis brevis muscle.[4] The patient agreed to participate in this trial before application of rTMS and gave informed consent to the study, which was approved by the local ethics committee.

During the application of rTMS, an EEG was recorded through F3, F4, C3, and C4, according to the International 10–20 system, in addition to monitoring MEPs on the bilateral obliquus externus abdominis muscles. Conventional EEGs recorded at rest before and after the rTMS trial did not show any abnormalities. Seizure was not seen during the measurement of motor threshold, although an EEG was not recorded. For the purpose of avoiding skin burn, radial notched electrodes were used while recording the EEG.

A focal slow wave (3–4 Hz) was recorded on C4 after the 4th stimulation of rTMS to the right prefrontal cortex on the first day of the trial. The slow wave disappeared at least 6 seconds later and reverted to an 8–10 Hz wave (fig 1). When rTMS to the right

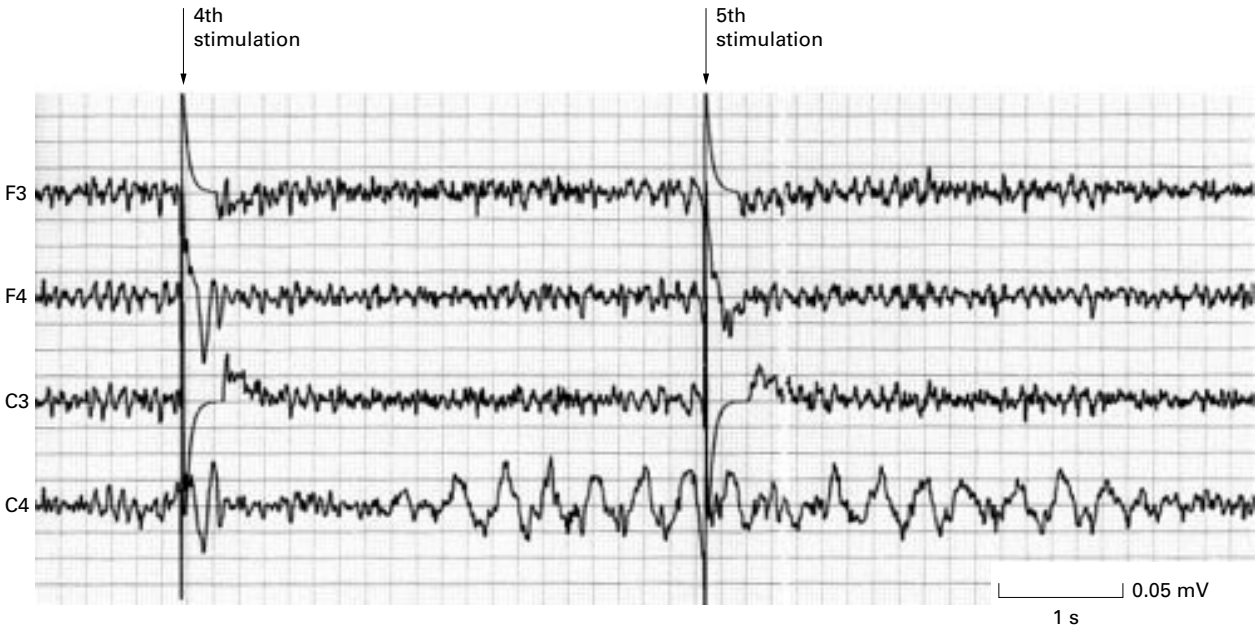

Figure 1 Change in the EEG during rTMS. After rTMS to the right prefrontal cortex had been initiated, the EEG recorded on C4 showed a slow wave. The slow wave disappeared at least 6 seconds later and reverted to an 8–10 Hz wave. This change was reproducible in rTMS performed on another day.

prefrontal cortex was restarted, a slowing wave of the EEG recurred and lasted longer after the 4th stimulation. This change did not occur during rTMS to the left prefrontal cortex. The recurring slow wave began and disappeared in the same manner.

The patient remained alert and seizure was not seen. These changes were reproducible in an rTMS trial performed on another day. We considered that these changes were induced by the application of rTMS and immediately discontinued the trial. During measurements of motor threshold and rTMS, the involuntary movement of the trunk and lower limbs continued and was unchanged. We could not assess the efficacy of rTMS for involuntary movement, because the trial study was discontinued in the middle of the protocol.

The slow wave activity was not present on the adjacent recording site. A possible explanation for our findings is that the spatial variation of the magnetic field intensity acting on the cortex may have resulted in an all or none response by the neurons. Another possibility is that neurons located in a responsive cortical region may have been more sensitive to the electric current induced by rTMS.

In the guidelines for rTMS,[6] monitoring an EEG is only a recommendation. In some case studies, the relation between seizures and EEG changes was investigated.[6 7] In most of those cases, the EEGs obtained immediately after the seizures showed slowing waves, but, they normalised within 1 or 2 days. In our case, a slow wave was seen without any accompanying clinical symptoms. However, we could not rule out the possibility of a consequent seizure if the rTMS trial had been continued in this patient. These findings suggest that further investigations of EEG changes during rTMS are required to apply rTMS safely.

M KANNO
T CHUMA
Y MANO
Rehabilitation Medicine, Hokkaido University Graduate School of Medicine, Nishi 7, Kita 15, Kita-ku, Sapporo, 060–8638, Japan

Correspondence to: Dr M Kanno.
m-kanno@umin.ac.jp

1 Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985;i:1106–7.
2 Mally J, Stone TW. Improvement in parkinsonian symptoms after repetitive transcranial magnetic stimulation. *J Neurol Sci* 1999;**162**: 179–84.
3 Siebner HR, Rossmeier C, Mentschel C, *et al*. Short-term motor improvement after subthreshold 5-Hz repetitive transcranial magnetic stimulation of the primary motor hand area in Parkinson's disease. *J Neurol Sci* 2000;**178**:91–4.
4 Pascual-Leone A, Rubio B, Pallardó F, *et al*. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 1996;**348**:233–7.
5 Wasserman EM, Wang B, Zeffiro TA, *et al*. Locating the moter cortex on the MRI with transcranial magnetic stimulation and PET. *Neuroimage* 1996;**3**:1–9.
6 Wasserman EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalogr Clin Neurophysiol* 1998;**108**: 1–16.
7 Wasserman EM, Cohen LG, Flitmann SS, *et al*. Seizures in healthy people with repeated safe trains of transcranial magnetic stimuli. *Lancet* 1996;**347**:825–6.

Early onset epileptic auditory and visual agnosia with spontaneous recovery associated with Tourette's syndrome

Potentially recoverable impairments of cognition, behaviour, and movement are integral to early onset epilepsies.[1] The classic epilepsy syndrome presenting as developmental regression is Landau-Kleffner syndrome, in which receptive aphasia and behavioural, cognitive, and motor impairments occur with centrotemporal discharges enhanced in sleep.[2] We report a novel biography of domain specific impairments and recovery in infantile spasms.

At 12 years of age the patient presented with Tourette's syndrome, with an extraordinary developmental history of epilepsy, regression, and recovery. He was normal until 6 months, being socially responsive, visually alert, reaching and transferring objects. Development slowed from 7 months. There was no relevant family history.

At 8 months runs of typical symmetric flexion spasms at intervals of 5–10 seconds, 3–4 times/day began. The EEG was disorganised, with bilateral very high amplitude (450 μV) activity and more left temporal area multifocal spikes and polyspikes, approaching classic hypsarrhythmia. ACTH (10 units daily and 40 units daily from 10–12 months) stopped the spasms after 2 weeks. Electroencephalography, CT, metabolic investigations, electroretinography, and visually evoked potentials were normal. CMV antibodies were present in blood, and virus in the urine.

Physical examination was normal. At 1 year an EEG showed excess of irregular slow activity without spikes. A sleep record was not performed.

One to two brief generalised seizures a week, consisting of slumping, losing consciousness and bilateral limb shaking, continued to 5 years of age. Occasional brief absences continued, were not treated, and stopped at 10.6 years. An EEG at 12 years was normal.

He lost smiling, visual following, and responsiveness at 7 months, 2 weeks before spasms were recognised. At 10.5 months development was assessed at a 7 month level. Development remained very slow to 3–3.5 years. At 3 years he could not understand speech or visually recognise his mother and performance skills were poor—for example, he could not thread beads. Cognition was assessed at less than half his chronological age, indicating educational needs as a child with severe learning difficulties. At 3.5 years speech understanding appeared, and by 4.5 years he was using a lot of speech. His family felt that "their child had returned".

On the Portage scale at 2.5 years of age, the raw scores and age level were socialisation 38: 1–2 years; language 7: 0–1 years: self help 24: 1–2 years; cognitive 18: 1–2 years; motor 68: 2–3 years. Non-motor skills were below 2 years with severe language retardation.

A Griffiths assessment at 3.10 years showed significant recovery: hearing and speech 3.8 years; performance 3.6 years;

locomotor 2.7 years; eye/hand coordination 2.8 years; personal/social 3.1 years

He transferred from special to mainstream education. Coordination problems continued.

He made good academic progress but with behavioural difficulties. Psychometric testing at 12 years showed above average performance and superior language scores with slow handwriting. He passed seven GCSEs and three A levels.

He had early problems with chewing and feeding, difficulties with drawing, buttons and laces, toiletting, and in using a knife and fork. Walking and running were abnormal and he could not use a bicycle. He showed slow alternating tongue movements, difficulty with manual gesture imitation, difficulty accessing hip movements, brisk tendon reflexes, and a few beats of clonus at the ankle. The motor picture was dominated by dyspraxia.

From year 2 he was restless with different compulsions—for example, switching lights on and off, scratching his teeth and nose, tooth grinding, hand fiddling, and face and shoulder movements. At 12 years, he had typical complex tics of his head, face and hands, and spasms, sometimes painful, of the jaw, legs, and abdomen. Vocalisations were either unintelligible and/or repeated words—for example, "zip".

Brain MRI at 12 years was normal.

Three features suggest a good outcome for this child with an otherwise typical presentation with infantile spasms: late age of onset, treatment response, and the lack of pre-existing pathology. Severe language impairment at 2.5 years might suggest a variant of Landau-Kleffner syndrome (acquired epileptic aphasia),[2] but atypically with very early onset and complete recovery. The recovery period suggests a combination of visual and auditory agnosia and apraxia, which could be regarded as global impairment. Selective cognitive deficits—for example, language impairments with epilepsy—are described, and transient loss of visual function, but not prolonged visual agnosia with infantile spasms. Although subclinical seizures in sleep may have been the cause, sleep studies were not performed.

Language and visual recovery from 3.5 years may indicate earlier cortical storing of visual and language information which was not accessible. Clinical,[1] neurophysiological,[3] and surgical[4] evidence supports this idea. This report supports the hypothesis that epilepsy denies access to information rather than inhibiting its acquisition.

We also propose that the early epileptic encephalopathy (impairments occurring with epilepsy which are not explicable on a structural basis) associated with infantile spasms selectively disturbs cognitive accessing of visual and auditory information temporarily after 6 months of age but permanently before that age.

Apraxia in epilepsy is well recognised,[5] but Tourette's syndrome is unexpected and may be an accidental association. When investigated, neither were driven by active epilepsy. No primary pathology was found and clinical manifestations, natural history, and imaging are not those of CMV encephalitis despite evidence of infection.

In conclusion, a boy with infantile spasms at 7–8 months developed severe global regression which seemed to be a combination of severe auditory and visual agnosia and apraxia which persisted for more than 2 years after prompt relief of infantile spasms but continuing mild generalised seizures. He was assessed as severely cognitively impaired. A total spontaneous cognitive recovery occurred from 3.5 years. These impairments seem to have been a pervasive effect of epilepsy (an epileptic encephalopathy), and suggest that if infantile spasms occur before 6 months there is a high risk of permanent impairment but if later there is potential for recovery. During the prolonged phase of "agnosia" information seems to have been acquired but was not accessible. The comorbidity of Tourette's syndrome is unexplained.

B G R NEVILLE
Neurosciences Unit, Institute of Child Health (UCL), The Wolfson Centre, Mecklenburgh Square, London WC1N 2AP, UK

H C SPRATT
General Hospital, Gloucester Street, St Helier, Jersey HE2 3QS, UK

J BIRTWISTLE
Principal Educational Psychologist, States of Jersey Education, PO Box 142, Jersey JE4 8QJ, UK
Correspondence to: Professor B G R Neville

1 Neville BGR. Reversible disability associated with epilepsy. *Brain Dev.* 1999;82–85.
2 Hirsch E, Marescaux C, Maquet P, *et al*. Landau-Kleffner syndrome: a clinical and EEG study of five cases. *Epilepsia* 1990;**31**:756–67.
3 Boyd SG, Rivera-Gaxiola M, Towell AD, *et al*. Discrimination of speech sounds in a boy with Landau-Kleffner syndrome: an intraoperative event related potential study. *Neuropaediatrics* 1996;**27**:211–15.
4 Vargha-Khadem F, Carr LJ, Isaacs E, *et al*. Onset of speech after left hemispherectomy in a 9 year old boy. *Brain* 1997;**120**:159–82
5 Neville BG, Boyd SG. Selective epileptic gait disorder. *J Neurol Neurosurg Psychiatry* 1995; **58**:371–3.

Motor evoked potentials from the external anal sphincter in patients with autosomal dominant pure spastic paraplegia linked to chromosome 2p

Hereditary spastic paraplegia (HSP) is the name given to a heterogeneous group of rare neurodegenerative disorders of the motor system characterised by slowly progressive spasticity and weakness of the lower limbs. About one third of patients with autosomal dominant pure spastic paraplegia (ADPSP) linked to chromosome 2p have lower urinary tract symptoms (LUTS) and additionally most of these patients also experience rectal urgency/urge incontinence (RUI) as well as sexual dysfunction.[1]

The direct motor pathway to the external anal sphincter may be studied by transcranial magnetic stimulation (TMS), evoking compound muscle action potentials (CMAPs) with cortical and sacral stimulation.[2 3]

This study was conducted to evaluate the motor evoked potentials (MEPs) from the external anal sphincter in patients with ADPSP linked to chromosome 2p and to obtain norminative data.

After informed consent was obtained 11 definitely affected patients from six different families with ADPSP linked to chromosome 2p and 12 normal controls were included. The median age for the patients was 41 (range 20–64) years, and for the controls 40 (range 21–60) years. Six patients had LUTS and RUI, five of whom previously underwent urodynamic evaluation including measures of the bulbocavernosus reflex (patient numbers A2, C4, C6, K10, and L11 in Neerup Jensen *et al*[1]). Five patients were without LUTS and RUI. Family details, clinical features, and urodynamic findings have been previously described.[4–1] The investigator was blinded to the urinary and bowel symptoms. The study was approved by the ethics committee.

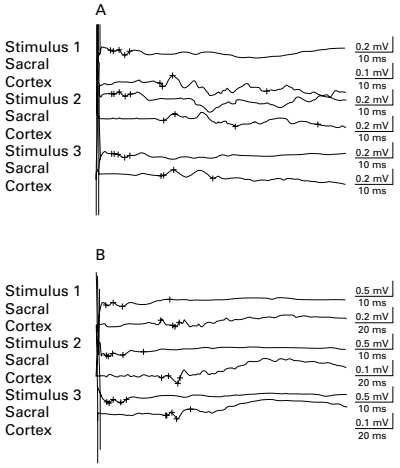

Figure 1 Cortical and sacral stimulation and CMAP from the external anal sphincter evoked in (A) a control person and (B) in a patient with ADPSP with LUTS and RUI. The stimulation is reproduced in three trials over the vertex and the sacral region.

Motor evoked potentials (MEPs) were elicited by cortical stimulation using a parabolic shaped coil, diameter 14 cm with a Twintop Magnetic Stimulator, and EMG responses obtained with a Keypoint EMG-machine (Dantec Medical Inc, Denmark). The compound motor action potentials (CMAPs) were recorded from the external anal sphincter using a disposable sphincter electrode (Dantec 13L81, Dantec Medical Inc, Denmark). The position of the electrode was anteroposterior to avoid cancelling of the motor potentials because of bilateral contraction from the right and left side of the external anal sphincter induced by cortical and sacral stimulations.

The cortical stimuli were applied near to the vertex in the area representing the lowest threshold for a motor contraction in the lower limbs measured in the right abductor hallucis (AH) muscle. The motor threshold (MT) was determined as the minimal stimulus intensity applied to the relevant cortical representation evoking at least three motor action potentials of five trials with an amplitude exceeding 50 μV. In some patients the MEP amplitudes were very small, and therefore MT determination was difficult. To ensure a sufficient stimulus intensity the AH muscle was selected for MT measures. The stimulus intensity was increased to 50% above MT for the AH muscle or to a level sufficient to evoke a reproducible contraction of the external anal sphincter. The patients and the controls were instructed not voluntary to contract the sphincter ("relaxed MEPs"). The cortical latency (CL) and amplitude of the CMAP were identified. The sacral stimulation was applied to the S2-S4 area using magnetic stimulation (maximum output) and the sacral latency (SL) and the central motor conduction time (CMCT=CL-SL) were calculated. The stimulations were performed in at least three individual trials with two runs to ensure reproducibility. In four patients the motor action potentials were hardly reproducible, and therefore an averaging technique was used in those patients. The results of MEPs

Table 1 Results (median (range)) of cortical and sacral stimulation in patients with ADPSP and normal controls

	Cortical stimulation		*Sacral stimulation*		
	Latency (ms)	*Amplitude (mV)*	*Latency (ms)*	*Amplitude (mV)*	*CMCT (ms)*
ADPSP (n=11)	28.0 (24.2–53.2)	0.04 (0.02–0.18)	5.2 (4.0–7.5)	0.15 (0.04–0.39)	22.8 (18.4–48.0)
ADPSP (without LUTS and RUI) (n=5)	26.0 (24.2–28.0)	0.07 (0.03–0.18)	5.8 (4.2–7.5)	0.15 (0.04–0.4)	20.7 (18.4–21.8)
ADPSP (with LUTS and RUI) (n=6)	33.6 (26.8–53.2)	0.03 (0.02–0.05)	5.1 (4.0–5.2)	0.18 (0.08–0.39)	29.0 (22.8–48.0)
Controls (n=12)	24.0 (22.0–29.5)	0.16 (0.04–0.42)	4.7 (3.0–7.8)	0.23 (0.02–0.59)	19.6 (16.5–23.5)

LUTS=Lower urinary tract symptoms; RUI=rectal urgency/urge incontinence; CL=cortical latency; CMAP=compound muscle action potential.
ADPSP with LUTS/RUI *v* ADPSP without LUTS/RUI:
CL p=0.02; CMAP amplitude p=0.03; CMCT p=0.01.
ADPSP with LUTS/RUI *v* control persons:
CL p=0.002; CMAP amplitude p=0.01; CMCT p=0.001.

obtained in upper and lower limb muscles are presented elsewhere.[4]

The results are presented as median (range), and the distributions were compared by the Kruskal-Wallis test. The level of significance was taken as 0.05.

Examples of cortical and sacral stimulation and CMAP from the external anal sphincter evoked in a control person and in a patient with LUTS and RUI are shown in figure 1. The results are shown in table 1.

The CL and the CMCT were significantly longer and the amplitude of CMAP at cortical stimulation was significantly lower in the patients with ADPSP with LUTS and RUI compared with the patients without these symptoms. The patients without LUTS and RUI presented no significant differences in CL, CMCT, or amplitude of the CMAP compared with the controls. The patients with LUTS and RUI presented significantly longer CL and CMCT and lower amplitudes of the CMAP than the control subjects. No significant differences in SL or amplitudes of CMAP at sacral stimulation were seen between the patients with ADPSP and the controls.

In this study we found that reproducible CMAPs could be obtained from the external anal sphincter using surface electrodes with cortical and sacral stimulation. Our normative values were similar to former studies.[2–3] Using TMS we showed that patients with LUTS and RUI presented longer CMCT and reduced amplitudes of the cortical evoked CMAPs, whereas patients without these symptoms showed no differences. As shown in table 1, there is little overlap between the two groups. The number of patients are small, but the results suggest that measurement of MEPs to the external anal sphincter may be a method to be used as a part of the evaluation of patients with supranuclear lesions and sphincter symptoms.

In neuropathological studies axonal degeneration was found to be maximal in the terminal portions of the longest descending and ascending tracts. Dorsal root ganglia, posterior roots, and peripheral nerves were normal.[5] Axonal degeneration of the corticospinal neurons, however, cannot solely explain the pathogenesis of the disease. Patients without LUTS and RUI presented normal CMCTs and only non-significantly reduced CMAsPs, despite the presence of severe spasticity. A reduced CMAP is suggestive of selective large fibre loss in the relevant spinal cord pathways; however, other mechanisms may be involved in the reduced CMAP, including a raised cortical threshold to TMS.

We conclude that MEPs from the external anal sphincter in patients with ADPSP linked to chromosome 2p with LUTS and RUI present longer CMCTs and lower CMAPs at cortical stimulation. These results may in part be related to the pathogenesis of the disease. MEPs from the external anal sphincter can be relatively easily evoked and may be a new useful method in the evaluation of patients with supranuclear lesions and RUI.

Financial support was obtained from Hartmann's Foundation, the Danish Medical Research Council, and the Danish Medical Association Research Fund.

P JENNUM
Department of Clinical Neurophysiology, Glostrup Hospital, University of Copenhagen, Ndr Ringvej, DK-2600 Glostrup, Denmark

L NEERUP JENSEN
Department of Gynaecology and Obstetrics, Gentofte Hospital, University of Copenhagen, Denmark

K FENGER
J E NIELSEN
Institute of Medical Biochemistry and Genetics, Department of Medical Genetics, Section of Neurogenetics. University of Copenhagen, The Panum Institute, Copenhagen, Denmark

A FUGLSANG-FREDERIKSEN
Department of Clinical Neurophysiology, University Hospital of Aarhus, Denmark

J E NIELSEN
Department of Neurology, The Neuroscience Centre, Rigshospitalet, Copenhagen, Denmark

Correspondence to: Dr P Jennum
Jennum@dadlnet.dk

1 Neerup Jensen L, Gerstenberg T, Kallestrup EB, *et al*. Urodynamic evaluation of patients with autosomal dominant pure spastic paraplegia linked to chromosome 2p. *J Neurol Neurosurg Psychiatry* 1998;**65**:693–6.
2 Ertekin C, Hansen CV, Larsson LE, *et al*. Examination of the descending pathway to the external anal sphincter and pelvic floor muscles by transcranial cortical stimulation. *Electroencephalogr Clin Neurophysiol* 1990;**75**:500–10.
3 Pelliccioni G, Scarpino O, Piloni V. Motor evoked potentials recorded from external anal sphincter by cortical and lumbo-sacral magnetic stimulation: norminative data. *J Neurol Sci* 1997;**149**:69–72.
4 Nielsen JE, Krabbe K, Jennum P, *et al*. Autosomal dominant pure spastic paraplegia: a clinical, paraclinical and genetic study. *J Neurol Neurosurg Psychiatry* 1998;**64**:61–6.
5 Bruyn RPM. The neuropathology of hereditary spastic paraparesis. *Clin Neurol Neurosurg* 1992 **94**(suppl):S16–8.

Call for guidelines for monitoring renal function and haematological variables during intravenous infusion of immunoglobulin in neurological patients

Intravenous immunoglobulin (IVIg) is widely used in the treatment of some neurological conditions thought to have an underlying immune basis. Controlled studies of IVIg have demonstrated benefit in Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and dermatomyositis. Treatment with IVIg has also been beneficial in myaesthenia gravis, multiple sclerosis, multifocal motor neuropathy with conduction block, polymyositis, Lambert-Eaton myaesthenic syndrome, stiff man syndrome, and Rasmussen's encephalitis.[1]

Various complications have been reported in the literature in association with IVIg therapy. These include headache, nausea, fever, rash, aches in the chest or limbs, anaphylaxis especially in association with IgA deficiency, leucopenia, neutropenia, autoimmune haemolysis, renal failure, thromboembolism, aseptic meningitis, and transmission of viral infections—for example, hepatitis C.[1] The therapeutic dose of IVIg in the treatment of neurological disease has been empirically set at 2 g/kg, conventionally divided into five daily doses of 400 mg/kg, although some authors have shown that a 2 day infusion of 1 g/kg is not associated with any higher incidence of side effects than the 5 day infusion.[2]

Despite the widespread use of IVIg in neurological centres in the United Kingdom, to our knowledge there exists no consensus for advice either on monitoring haematological and renal function in patients pretreatment and post-treatment with IVIg, nor on the merits of shorter infusion periods of IVIg. Both of these factors have considerable cost implications for the National Health Service (NHS).

We have retrospectively examined the records of 21 patients admitted to a regional neurology centre (Hurstwood Park Neurological Centre), over an 18 month period. As several of these patients had multiple courses of IVIg treatment, the records contained 71 courses of treatment, although complete haematological data pretreatment and post-treatment was only available on 35 of these. The conditions treated included Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, and myaesthenia gravis. The average age of patients was 51 years (range 22–86 years). Eight patients had indications of possible renal dysfunction (based on one or more abnormal blood urea and creatinine concentration) within 6 months before the first course of treatment. All courses given were at 0.4 g/kg Sandoglobulin (Novartis)for 5 days. A course of treatment was stopped or delayed eight times out of 71 courses: the reasons stated included thombocytopenia (one patient: platelet count<100×10^9/l, normal range 150–400×10^9/l); leucopenia (three patients: white cell count<1.7×10^9/l, normal range 4–11×10^9/l), neutropenia (three patients: neutrophil count<1.5×10^9/l, normal range 2–7.5×10^9/l); and renal failure (one patient: sodium 134 mM, normal range 132–144 mM, potassium 5.6 mM, normal range 3.5–5.5 mM, urea 20 mM, normal range 2.5–6.7 mM, and creatinine 330 μM, normal

range 60–120 μM]). Other adverse effects noted which did not delay or stop treatment included tachycardia (one patient), fall in haemoglobin (one), persistent pyrexia (one), nausea and vomiting (four), limb or chest pain (four), rigors (two), and headache (two). It was noted that there was no consensus on the level of leucopenia, neutropenia, raised urea, or creatinine at which treatment was discontinued among the six consultant neurologists at the centre. During a 5 day course, the white cell count was noted to fall below 4×10^9/l in 12 patients and the neutrophil count to below 2.0×10^9/l in eight patients. Urea and creatinine concentration only became abnormal in one patient (who developed renal failure requiring haemodialysis) whose renal function was mildly impaired before treatment (sodium 133 mM, potassium 4.6 mM, urea 7.0 mM, and creatinine 138 μM). In all patients with noted haematological derangement secondary to IVIg treatment, subsequent blood monitoring 14 days after stopping treatment showed a return to normal values.

The number of patients who had abnormal blood variables during this retrospective study suggests a need to establish guidelines for monitoring haematological and renal variables during IVIg therapy. Furthermore, given the cost implications of an abortive course of IVIg treatment, guidelines for a tolerable level of leucopenia, neutropenia, or urea/creatinine derangement during a standard 5 day course of IVIg also needs to be established. It may well be that neutropenia during IVIg treatment is transient and reversible, as suggested by this study, and if validated, there would be an argument against the need for regular haematological monitoring during IVIg therapy. This argument is supported by the findings of Koffman *et al*,[3] who retrospectively reviewed the records of 46 patients with neuromuscular disease receiving standard courses of IVIg (Gamimune N (Bayer) 2 g/kg) compared with 23 patients given placebo infusions of dextrose in water. In this study leucopenia, neutropenia, and lymphopenia were noted in a large proportion of patients treated with IVIg. Despite this no significant side effects—for example, infection—resulted and all haematological derangements were transient.

Furthermore, consensus needs to be established on the effect of IVIg formulation and risk of sucrose nephropathy (sucrose is used as a stabiliser in some IVIg preparations). Some previous case reports have suggested a link between the use of high sucrose formulations of IVIg (for example, Sandoglobulin (Novartis)) and subsequent renal failure compared with the use of lower sugar or glycine based formulations.[4] However, a recent report by Levy and Pusey[5] comparing Vigam (BPL; 0.5 g sucrose/g immunoglobulin) and Sandoglobulin (Novartis: 1.76 g sucrose/g immunoglobulin) in various indications has shown no such correlation between concentration of sucrose stabiliser in IVIg and propensity to cause renal failure. In their study of 119 patients given 287 courses of IVIg, eight patients (6.7%) showed a deterioration in renal function regardless of preparation used. On this basis, they concluded that all patients given IVIg should have renal function monitored before, during, and 4–5 days after treatment. This should be compared with the study of Koffman *et al*,[3] where none of the 46 patients given the same preparation of high dose IVIg had renal dysfunction.

Our current practice, based on the results of this audit and the literature available, is to check the renal function of all patients before IVIg therapy. Those in whom the renal function is mildly abnormal (normal sodium and potassium, urea 7–8 mM, and creatinine 120–150 μM) have their renal function monitored during and 5 days after IVIg treatment and are currently receiving low sucrose or no sucrose (Octogam(Octopharma)) IVIg formulations. Patients with more seriously impaired renal function are not being considered for IVIg therapy; alternative modes of treatment—for example, plasmapharesis—could be considered for this subgroup. Haematological function is also checked before IVIg therapy; if normal, no further monitoring is carried out during or after IVIg treatment. If there is evidence of mild leucopenia, neutropenia, or thrombocytopenia before IVIg, the full blood count is monitored on a daily basis during treatment and once more 5 days after treatment. Patients with more severe blood derangement (platelets$<100\times10^9$/l, neutrophil count$<1\times10^9$/l, and leucocyte count$<2\times10^9$/l) are not being considered for IVIg therapy and again alternative modes of therapy would be considered.

A consensus statement on the recommended duration of treatment course (1–2 days *v* 5 days) and the requirements for blood monitoring during IVIg infusion will require further study and collaborative audit across the many neurological centres in the United Kingdom using this form of therapy. We think that the potential cost implications and side effect profile of IVIg justify a call for such a study.

We thank Professor Richard Hughes for his help in the preparation of this manuscript.

N P S BAJAJ
N HENDERSON
R BAHL
K STOTT
R E CLIFFORD-JONES
Departments of Neurology and Pharmacy, Hurstwood Park Neurological Centre (HPNC), Hurstwood Lane, West Sussex, UK

Correspondence to: Dr N P S Bajaj, Department of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1 3BG, UK
narinderbajaj@compuserve.com

1 Brannagan TH, Nagle K, Lange DJ, *et al*. Complications of intravenous immune globulin treatment in neurologic disease. *Neurology* 1996;**47**:675–77.
2 Dalakas MC. Mechanism of action of intravenous immunoglobulin and therapeutic considerations in the treatment of autoimmune neurologic diseases. *Neurology* 1998;**51**(S5): S2–8.
3 Koffman BM, Dalakas MC. Effect of high-dose intravenous immunoglobulin on serum chemistry, haematology, and lymphocyte subpopulations: assessments based on controlled treatment trials in patients with neurologic diseases. *Muscle Nerve* 1997;**9**:1102–7.
4 Haskin JA, Warner DJ, Blank DU. Acute renal failure after large doses of intravenous immunoglobulin. *Annals of Pharmacotherapy* 1999; **33**:800–3.
5 Levy JB, Pusey CD. Nephrotoxicity of intravenous immunoglobulin. *Q J Med* 2000;**93**: 751–5.

Neuropsychological effects of pallidotomy in patients with Parkinson's disease

Whether patients with Parkinson's disease develop cognitive impairments or improvements after ventral pallidotomy is still a debated issue.[1] Recent studies produced contradictory findings which may have resulted from methodological factors such as differences in surgical techniques, neuropsychological assessments, duration of follow up, and the lack of evaluations of non-operated controls with Parkinson's disease.[1]

We assessed a consecutive series of 27 patients with Parkinson's disease who received unilateral pallidotomy using the microelectrode registration technique.[2] Sixteen of these patients received a 3–6 month follow up evaluation, and 10 of them received a 12 month follow up evaluation. They were compared with a non-operated control group of 20 patients with Parkinson's disease matched for age, severity of extrapyramidal symptoms, and overall cognitive status who received the same neuropsychological evaluation at baseline and 12 months later. The neuropsychological examination included the Raven's progressive matrices, the Wisconsin card sorting test (WCST), the controlled oral word association test, the Buschke selective reminding test, the Benton visual retention test, the digit span, and the Perdue pegboard.

No significant differences between the pallidotomy and the control groups were found for age (years (SD) pallidotomy group 56.3 (6.9), control group 59.3 (7.9)), sex (pallidotomy group 50% women, control group: 50% women), years of education (years (SD) pallidotomy group10.7 (2.7), control group: 11.4 (4.1)), baseline levodopa equivalent dosage, and UPDRS total scores (table 1). All patients were right handed.

Sixteen patients with Parkinson's disease who underwent unilateral pallidotomy received a 3–6 month follow up. A repeated measures multivariate analysis of variance (MANOVA) for the neuropsychological variables comparing baseline versus 3–6 month

Table 1 Neurological and neuropsychological findings

	Pallidotomy group		*Control group*	
	Initial evaluation	*Follow up evaluation*	*Initial evaluation*	*Follow up evaluation*
Mini mental state examination	26.4 (3.4)	25.3 (3.3)	26.3 (3.3)	27.5 (2.2)
UPDRS motor score	15.4 (7.8)	10.8 (5.3)	18.8 (15.8)	15.1 (9.0)
Levodopa dosage	785 (379)	775 (429)	590 (346)	890 (711)
Raven's progressive matrices	39.9 (33.8)	53.9 (36.1)	59.8 (36.5)	62.2 (34.3)
Wisconsin card sorting test	3.7 (2.1)	4.0 (2.5)	4.6 (1.9)	4.9 (1.9)
Verbal fluency	33.0 (8.9)	37.3 (6.4)	38.8 (9.8)	41.0 (13.4)
Buschke total recall	65.4 (22.2)	69.4 (17.5)	76.7 (18.1)	70.5 (15.3)
Buschke delayed	3.3 (3.1)	5.5 (3.0)	6.8 (3.0)	5.8 (2.5)
Benton visual retention test	5.7 (3.0)	7.1 (2.6)	7.7 (2.0)	7.5 (2.1)
Digits forward	5.3 (0.8)	5.0 (1.0)	5.7 (1.1)	5.6 (0.9)
Digits backwards	3.6 (0.8)	3.8 (0.8)	4.2 (1.0)	4.4 (1.0)
Perdue pegboard test*	14.0 (5.5)	17.9 (2.6)	19.3 (5.5)	18.9 (6.4)

Values are means (SD).
*$F(1,28)=8.84$; $p<0.01$.

follow up evaluation showed no significant overall time effect ($F(7,56)=1.01$; NS). There was a significant time effect for the Perdue pegboard test ($F(1,14)=30.9$; $p<0.0001$), with a significant improvement in manipulative dexterity over time. A repeated measures MANOVA for the neuropsychological variables comparing patients with either a left (n=7) or right (n=9) pallidotomy showed no significant group effect ($F(1,7)=0.05$; NS), time effect ($F(1,7)=1.03$; NS), or group×time interaction ($F(8,56)=0.22$; NS).

A repeated measures MANOVA for the neuropsychological variables for the 10 patients who had undergone pallidotomy (six right, four left) with a 12 month follow up and the 20 non-operated patients with Parkinson's disease did not show a significant group effect ($F(1,23)=0.29$; NS), time effect ($F(1,23)=0.43$; NS), or group× time interaction ($F(7,161)=0.18$; NS). On the other hand, there was a significant group×time interaction for the Perdue pegboard test ($F(1,28)=8.84$; $p<0.01$): the pallidotomy group showed a significant improvement during the follow up period, whereas the control group had a slight decline.

Most studies on the cognitive sequelae of pallidotomy could not show significant neuropsychological deficits after surgery,[3] and the only studies that to our knowledge included a non-operated Parkinson's disease control group (Perrine *et al*[4] and the present one) confirmed this finding. On the other hand, Lang *et al*[5] reported some cognitive impairments after ventral pallidotomy; and differences in neuropsychological outcome measures may account for this discrepancy. We examined the neuropsychological sequelae of pallidotomy in a consecutive series of 16 patients with Parkinson's disease, 10 of whom had a 1 year follow up evaluation. When compared with a group of 20 patients with Parkinson's disease matched for MMSE scores and age who did not receive a pallidotomy, no significant between group differences were found in the rate of cognitive changes. On the other hand, the pallidotomy group showed a significant improvement on a task measuring manual dexterity compared with the control Parkinson's disease group. The question now arises as to why pallidotomy in Parkinson's disease does not produce significant cognitive deficits, given that some case reports described various intellectual problems after spontaneous pallidal lesions. Firstly, most lesion studies included patients with bilateral lesions, whereas pallidotomy is usually performed on one side only. The few reports of bilateral pallidotomy in Parkinson's disease described important cognitive sequelae in some of the patients. Secondly, pallidotomy usually produces a small and localised lesion, whereas spontaneous pallidal lesions are usually larger and often involve white matter tracts next to the pallidum. Finally, some of our pallidotomy patients were tested three or four times, compared with only two neuropsychological evaluations for the control group, which may have produced some learning effects.

This study was partially supported by a grant from the Raul Carrea Institute of Neurological Research-FLENI and the Fundación Perez Companc. We thank Fred Bylsma PhD for his useful suggestions.

G KUZIS
L SABE
C TIBERTI
F DORREGO
S STARKSTEIN
Department of Neuropsychiatry, Raúl Carrea Institute of Neurological Research FLENI, Montañeses 2325, 1428 Buenos Aires, Argentina

M MERELLO
S STARKSTEIN
Department of Clinical Neurology

Correspondence to: Dr G Kuzis
ses@fleni.org.ar

1 Scott RB. Cognitive function and pallidotomy. *J Neurol Neurosurg Psychiatry* 1998;**65**:148.
2 Merello M, Nouzeilles M, Kuzis G, *et al*. Unilateral radiofrequency lesion versus electrostimulation of posteroventral pallidum: a prospective randomized comparison. *Mov Disord* 1999;**14**: 50–6.
3 Lund-Johansen M, Hugdahl K, Wester K. Cognitive function in patients with Parkinson's disease undergoing stereotaxic thalamotomy. *J Neurol Neurosurg Psychiatry* 1996;**60**:564–71.
4 Perrine K, Dogali M, Fazzini E, *et al*. Cognitive functioning after pallidotomy for refractory Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1998;**65**:150–4.
5 Lang AE, Lozano A, Tasker R, *et al*. Neuropsychological and behavioral changes and weight gain after medial pallidotomy. *Ann Neurol* 1997;**41**:834–5.

Response to botulinum toxin in a case of rigid spine syndrome

First described by Dubowitz in 1965,[1] rigid spine syndrome represents an axial congenital merosin positive muscular dystrophy with early, predominant rigidity of the spine as its main characteristic trait. The illness begins at an early age with a delay in motor development, and affects more boys than girls; however, in some cases onset occurs slightly later when weakness of proximal limb muscles appears in a previously otherwise asymptomatic child. In all cases a limitation of neck and trunk flexion develops and scoliosis appears either simultaneously or in the ensuing years; later on the disease may progress slowly or tend to stabilise. Other features that accompany the musculoskeletal signs are respiratory disturbances and cardiac changes.[2] Recently, a first locus for this syndrome has been identified on chromosome 1p.[3] In laboratory studies serum creatine kinase concentrations can be raised. Electromyographic studies of paracervical musculature, trapezium, deltoid, biceps, and quadriceps show a myopathic pattern with normal nerve conduction velocities. Biopsy findings disclose non-specific myopathic changes with descriptions of type I fibre predominance, type II fibre predominance and fibre type disproportion; electron microscopic studies have detected the presence of Z band streaming.

It is important to distinguish rigid spine syndrome from other diseases in which rigidity of the spine can appear, such as Duchenne and Becker's muscular dystrophies, and principally from Emery-Dreifuss muscular dystrophy and from early onset ankylosing spondylitis, as prognoses are different. The rigid spine sign has also been reported in Bethlem myopathy and congenital myopathies such as nemaline myopathy. As in other muscular dystrophies, no more than supportive care can be offered to patients with rigid spine syndrome; surgical correction has been attempted on one occasion with success.[4] Here we report a good response to botulinum toxin type A (BOTOX) treatment in a young man with rigid spine syndrome.

A 15 year old boy born at term, with congenital hypospadias surgically corrected and normal psychomotor development, was being studied by an endocrinologist because of short stature (mother's stature 145 cm, father's stature 169 cm) who noticed progressive neck flexion limitation and referred him to our institution. At admission on 8 July 1996, he complained of back pain since the previous year, which was more severe at rest; his mother had noticed a gait disturbance and that his back was progressively bending forward. General examination was normal; neurological examination showed no abnormal findings, and strength was completely preserved in all four limbs. He had marked postural kyphosis and contracture of neck extensors severely limiting movement in the anterior and lateral senses; hip flexion was severely affected (below 30°); no pain was produced by sacral manoeuvres. Radiological examination of the cervicothoracic spine showed scoliosis without vertebral malformations, 65° cervical lordosis involving C2 to C7, and a 55° thoracic kyphosis involving T3 to T12. Routine blood testing showed no abnormalities and creatine kinase concentrations were normal; autoantibodies routinely tested were negative. Complete spine MRI studies ruled out vertebral malformations. An ECG and radiography of the chest were normal. Radiological study of sacral joints was normal and the patient was not HLA-B27 positive. An EMG study showed a myopathic pattern (paraspinal musculature, periscapular musculature, and right quadriceps) with

Table 1 Schedule, place, and amount of botulinum toxin injection

	1996		*1997*			*1998*
Injected muscle	*July*	*October*	*January*	*May*	*September*	*January*
Trapezium	50 UI BOTOX® (each trapezium)	30 UI BOTOX® (right trapezium)	30 UI BOTOX® (each trapezium)	20 UI BOTOX® (each trapezium)	20 UI BOTOX® (each trapezium)	10 UI BOTOX® (each trapezium)
Esternocleidomastoid (ECM)		30 UI BOTOX® (each ECM)	30 UI BOTOX® (Each ECM)			
Paracervical musculature					20 UI BOTOX® (each side)	15 UI BOTOX® (each side)

The patient received 50 IU BOTOX® (Allergan) in three different locations of each trapezium on 17 July 1996; on 24 October 1996, 30 IU BOTOX were administered in each esternocleidomastoid and 30 IU in right trapezium; on 22 January 1997 30 IU BOTOX were given in each esternocleidomastoid and trapezium; on 21 May 1997 20 IU BOTOX were given in each trapezium; on 25 September 1997 40 IU BOTOX were given in each trapezium and bilateral paracervical musculature (total 80 IU); on 15 January 1998 10 IU BOTOX were given in each trapezium and 30 IU in paracervical musculature bilaterally.

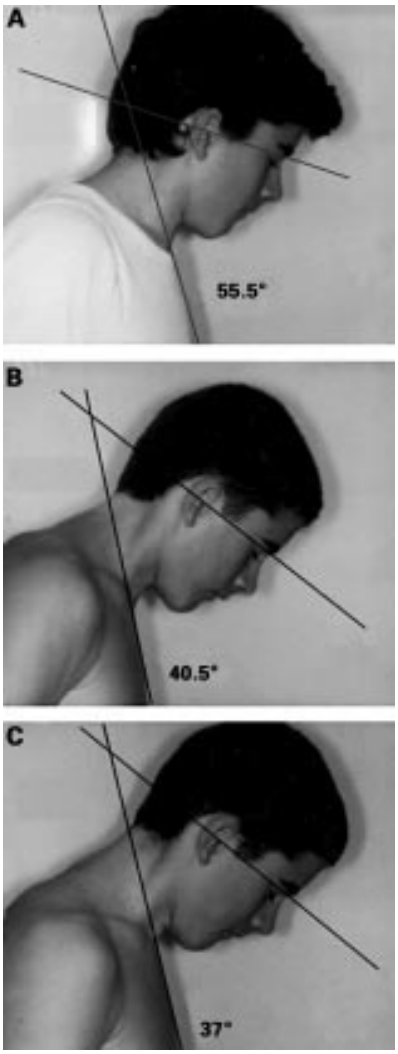

Figure 1 Three different photographs in which progressive amelioration in neck flexion is seen. To make this change objective, we measured the angle between a line joining nasion and tragus and another prolonging the sternum surface. (A) Photograph taken on 22 January 1997. (B) Photograph taken on 24 September 1997. (C) Photograph taken on 15 January 1998.

no abnormalities in nerve conduction. A biopsy of paraspinal musculature was performed and the neuropathological study of the muscle showed non-specific myopathic changes, including slight variability in muscle fibre size, occasional moth eaten fibres, and dilatations of the smooth endoplasmic reticulum, which were filled with fine granular material. The distribution and percentage of fibre types was preserved and no abnormalities in mitochondria and myofibres were seen. Immunohistochemistry to dystrophins, utrophin, and spectrin was normal. A diagnosis of rigid spine syndrome was made and botulinum toxin therapy was begun; with the aim of diminishing the imbalance between the neck flexor and extensor muscular groups to avoid fixed neck extension; for this reason we targeted muscles involved in head extension, principally the trapezium and secondly the esternocleiodomastoid and the paracervical musculature (table 1). During BOTOX therapy continuous improvement in neck flexion was seen, which was also perceived by the patient (fig 1). The radiological and functional measurements confirmed this assertion: in January 1996 the distance from chin to sternum was 10 cm in maximum neck flexion, in December 1997 this distance was 3 cm and in June 1999 the patient was able to touch his sternum with his chin. In march 1999 the patient developed myocarditis, with acute thoracic pain two weeks after a sore throat, increased creatine kinase concentrations, and electrocardiographic changes, with good recovery in 1 week. An echocardiogram performed 3 months later was normal and serology for Coxsackie virus was positive.

BOTOX is the trade mark of the commercialised typeA toxin of *Clostridium botulinum*; BOTOX causes muscle paralysis by acting at nerve endings and blocking presinaptically the release of quanta of acetylcholine[5]; this muscular paralysis is reversible and can ameliorate symptoms in patients with muscle spasms appearing as a manifestation of multiple neurological disturbances,[6–8] including myopathies.[9 10] In some situations this amelioration may become long lasting, and patients will not require further injections.[11] The American Academy of Neurology recommends its therapeutic use in blepharospasm as a primary form of therapy; its use is accepted in cervical dystonia, adductor spasmodic dysphonia, jaw closing dystonia, and in hyperkinesis of hemifacial spasm; its use is considered promising in jaw opening and deviation dystonia, abductor spasmodic dysphonia, and in other focal dystonias.

The origin of spine stiffness in rigid spine syndrome is not well understood. Shortening of paraspinal ligaments or shortening of muscle fibres due to myofibrilar disorganisation have been invoked as possible origins of stiffness[12]; weakness of neck flexors can make this group of muscles incapable of counteracting extensor strength, finally causing spinal rigidity and cervical lordosis. Botulinum toxin may have an important part to play in preventing development of contractures and avoiding stiffness, not only in a symptomatic way, but also in a curative manner, as in our patient.

We thank Ms Julie Myers and Mr Josep Graells for linguistic assessment.

J SASTRE-GARRIGA
M TINTORÉ
X MONTALBAN
Unitat de Neuroimmunologia Clínica, Servei de Neurologia, Escola d'Infermeria, 2ª planta, Hospital Vall d'Hebron, Passeig de la Vall d'Hebron 119–129, Barcelona 08035, Spain

J BAGÓ
Servei de Cirurgia Ortopèdica i Traumatologia

I FERRER
Unidad de Neuropatologia, Hospital Príncipes de España, Hospitalet de Llobregat, Spain

Correspondence to: Dr J Sastre-Garriga
32449jsg@comb.es

1 Dubowitz V. "Pseudo" muscular dystrophy. In: Research Committe of the Muscular Dystrophy Group of Great Britain, eds. *Research in muscular dystrophy: Proceedings of the Third Symposium*. London: JB Lippincot, 1965:57–73.
2 Poewe W, Willeit H, Sluga E, *et al*. The rigid spine syndrome—a myopathy of uncertain nosological position. *J Neurol Neurosurg Psychiatry* 1985;**19**:105–8.
3 Moghadaszadeh B, Desguerre I, Topaloglu H, *et al*. Identification of a new locus for a peculiar form of congenital muscular dystrophy with early rigidity of the spine, on chromosome 1p35–36. *Am J Hum Genet* 1998;**62**:1439–45.
4 Giannini S, Ceccarelli F, Granata C, *et al*. Surgical correction of cervical hyperextension in rigid spine syndrome. *Neuropediatrics* 1988;**19**: 105–8.
5 Brin MF. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. *Muscle Nerve* 1997;**20**(suppl 6):146–68.
6 Davis D, Jabbari B. Significant improvement of stiff-person syndrome after paraspinal injection of botulinum toxin A. *Mov Disord* 1993;**8**:371–3.
7 Giladi N, Honigman S. Botulinum toxin injections to one leg alleviate freezing of gait in a patient with Parkinson's disease. *Mov Disord* 1997;**12**:1085–106.
8 Grazko MA, Polo KB, Jabbari B. Botulinum toxin A for spasticity, muscle spasms and rigidity. *Neurology* 1995;**45**:712–17.
9 Doyle M, Jabbari B. Hypertrophic branchial myopathy treated with botulinum toxin type A. *Neurology* 1994;**44**:1765–6.
10 Nix WA, Butler IJ, Roontga S, *et al*. Persistent unilateral tibialis anterior hypertrophy with complex repetitive discharges and myalgia: report of two unique cases and response to botulinum toxin. *Neurology* 1992;**42**:602–6.
11 Heinen F, Wissel J, Philipsen A, *et al*. Interventional neuropediatrics: treatment of dystonic and spastic muscular hyperactivity with botulinum toxin A. *Neuropediatrics* 1997;**28**:307–13
12 Lotz BP, Stügben JP. The rigid spine syndrome: a vacuolar variant. *Muscle Nerve* 1993;**16**:530–6.

"Hot cross bun" sign in a patient with parkinsonism secondary to presumed vasculitis

Brain MRI is an important tool in the investigation of patients with unusual parkinsonian syndromes. The "hot cross bun" sign is a radiological sign which has been said to be highly specific for multiple system atrophy.[1] However, we now report on a patient with the hot cross bun sign who presented with parkinsonism secondary to presumed vasculitis.

Our patient was a 31 year old woman who was referred with an 18 month history of double vision, balance problems, and deafness. Brain MRI performed 9 months before this admission had demonstrated a non-enhancing swelling of the pons (fig 1 A). She had not responded to a 4 week course of oral adrenocorticotropic hormone treatment at that time. On admission to our unit there had been no change in her symptoms. On examination she had mild cognitive impairment (mini mental state score 24/30) and a labile affect. She had a bilateral horizontal supranuclear gaze palsy. In addition she had a right upper motor neuron facial palsy and bilateral sensorineural deafness (confirmed by audiometry). Examination of her limbs showed axial and bilateral limb rigidity. She exhibited bradykinesia but did not have a resting limb tremor. She had signs of cerebellar ataxia in all her limbs and walked with a broad based gait requiring the assistance of another person. Limb power and sensation were normal and her plantars were flexor. There was no evidence of dysautonomia or rheumatological disease.

Blood investigations showed a raised erythrocyte sedimentation rate at 36 mm/hour, raised serum IgG at 21.6 g/l (with a polyclonal pattern on electrophoresis), a positive rheumatoid factor titre (>1:320), a positive speckled ANA titre (>1:640), and positive anti-Ro antibodies (33 units). Schirmer's test, thyroid function tests, copper studies, and manganese were all negative or normal. Brain MRI showed severe atrophy of the medulla, pons, cerebellum, and middle cerebellar peduncles with cross shaped T2 signal hyperintensity within the pons (hot cross bun sign) and high signal change in the middle cerebellar peduncles (fig 1 B). There were no supratentorial lesions. Phase contrast MR angiography of the brain was normal. Examination of CSF showed no increase in cells

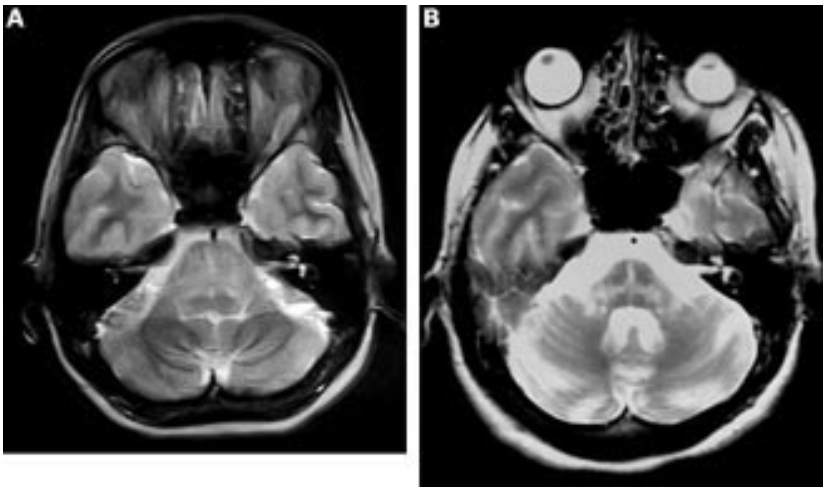

Figure 1 (A) Initial T2 weighted brain MRI of the patient disclosed non-enhancing pontine swelling. (B) Nine months later T2 weighted MRI showed severe atrophy of the medulla, pons, cerebellum, and middle cerebellar peduncles with cross shaped T2 signal hyperintensity within the pons (hot cross bun sign) and high signal change in the middle cerebellar peduncles.

and normal protein, lactate, and glucose; however, CSF electrophoresis demonstrated intrathecal oligoclonal IgG production. The patient was treated with pulsed intravenous cyclophoshamide and a reducing course of steroids but did not improve significantly. There has been no further deterioration since treatment.

The hot cross bun appearance in multiple system atrophy is due to loss of pontine neurons and myelinated transverse pontocerebellar fibres with preservation of the corticospinal tracts which run craniocaudally.[2] Our patient presented with a severe parkinsonian syndrome associated with cerebellar and brain stem dysfunction. The absence of dysautonomia together with the initial MRI appearance of swelling of the pons made the diagnosis of multiple system atrophy extremely unlikely. Although she had a supranuclear gaze palsy her scans were not typical of progressive supranuclear palsy.[1] The serological and CSF findings together with initial pontine swelling suggested probable vasculitis, a recognised cause of parkinsonism.[3] Wallerian degeneration secondary to vasculitic infarction results in hyperintensity on T2 weighted MRI.[4] The hot cross bun sign in our patient may reflect selective wallerian degeneration of transverse pontocerebellar fibres. Thus, the clinical findings of this case highlight the need to consider alternative diagnoses to multiple system atrophy in patients with the hot cross bun sign.

M M K MUQIT
D MORT
K A MISZKIEL
R A SHAKIR

Division of Neuroscience and Psychological Medicine, Imperial College School of Medicine at Charing Cross Hospital, Fulham Palace Road, London, W6 8RF, UK

Correspondence to: Dr R A Shakir

1 Schrag A, Good CD, Miszkiel K, *et al*. Differentiation of atypical parkinsonism syndromes with routine MRI. *Neurology* 2000;**54**:697–702.
2 Schrag A, Kingsley D, Phatouros C, *et al*. Clinical usefulness of magnetic resonance imaging in MSA. *J Neurol Neurosurg Psychiatry* 1998;**65**: 65–71.
3 Walker RH, Spiera H, Brin MF, *et al*. Parkinsonism associated with Sjogren's syndrome: three cases and a review of the literature. *Mov Disord* 1999;**14**:262–8.
4 Ramsey R, ed. *Neuroradiology*. 3rd ed. Philadelphia: WB Saunders, 1994:514.

BOOK REVIEWS

Charcot-Marie-Tooth disease. A practical guide. Compiled by CMT INTERNATIONAL UK (Pp 113, £10.00). Published by CMT International UK, Penarth, 2000. ISBN 0 9533883 0 1.

Charcot-Marie-Tooth disease. A practical guide, is a book compiled by CMT International UK with the aim of providing an overview of Charcot-Marie-Tooth disease (CMT) with a particular emphasis on providing practical day to day advice for living with the disease. It is aimed at doctors and patients and other people involved with CMT . It is well written and excellently presented and provides a range of information that the intended audience will find invaluable.

The book is divided into three main sections. The first section deals with genetic and medical issues. The known genetic variants of the disease are well described and accurate except for one mistake stating that the gene duplication that causes CMT1a is on chromosome 22 when it is actually on chromosome 17. I thought the section covering CMT inheritance was particularly well presented and illustrated using simple diagrams to explain the various inheritance mechanisms. There was also a very useful glossary of scientific and medical terms in this section.

The second section deals with living with CMT. This covers many important areas for the patient including coming to terms with the diagnosis, care of the feet, pain control, and secondary complications. Foot deformities and their surgical correction were particularly well covered.

The third section deals with practical issues including finding work, having a baby, driving, and CMT and aids to daily living. This section is particularly useful in providing contact details for many different organisations who will help patients. All three sections are supported by informative appendices.

This book is an excellent patient oriented guide, full of useful information and contacts. It will be a particularly useful book to recommend to newly diagnosed patients.

MARY REILLY

Conduct disorders in childhood and adolescence. Edited by JONATHAN HILL and BARBARA MAUGHAN (Pp 569, £39.95). Published by Cambridge University Press, Cambridge, 2000. ISBN 0 521 78639 8.

This is an extremely interesting and informative book that does justice to the complexity of perspectives on child and adolescent conduct problems. It is evident that considerable attention was given to shaping this book, which succeeds in being more than a collection of papers on conduct problems. Individual authors have been careful to introduce their particular area of interest to readers unfamiliar with their field. For example, Herbert and Martinez's chapter on "Neural mechanisms underlying aggressive behaviour" is a lucid account available to a novice reader. Throughout the book there are discussions that refer to other theoretical perspectives, thus illuminating the theoretical, methodological, and clinical issues. Reading the book is rather like a mental brass rubbing in that the reader's patience is rewarded by the emergence of an increasingly complex but fascinating pattern of relations between biological, genetic, neuropsychological, social, interactional and psychological stand points.

The book moves back and forth between chapters that contextualise, for example the historical perspective offered by Costello and Angold's chapter, to consideration of very specific mechanisms such as Lynham and Henry's chapter on the role of neuropsychological deficits and Petit, Pohlaha, and Mize's chapter on perceptual and attributional processes. Each chapter gives a critical view of relevant research and raises methodological concerns. The spirit of the book is captured in Hill's chapter on biosocial influences, in which he conveys a sense of curiosity about the interaction between biological and social phenomena and how that might be further investigated.

Kazdin gives careful attention to treatment of conduct disorders in an excellent chapter. Le Marquand, Tremblay, and Vitaro consider issues of prevention and Knapp's chapter brings forward the economic costs of conduct disorder.

In conclusion I return to the subjects of this work, the children and young people, and their families who experience great emotional distress and difficulty, very often in the context of socioeconomic hardship. Inclusion of qualitative research would have further enriched this book, by bringing their voices more directly into the important debates so elegantly presented. It deserves to become a standard work, available widely to all clinicians and researchers interested in this field.

MOIRA DOOLAN

Half a brain is enough: the story of Nico. Edited by ANTONIO M BATTRO (Pp 118, £12.95). Published by Cambridge University Press, Cambridge, 2000. ISBN 0 521 78307 0.

This short book describes the fascinating recovery and remarkable neurocognitive compensation of Nico, a little boy who at the

age of three underwent a right hemispherectomy for intractable epilepsy. Although such cases are not now rare, the emphasis on how the neuropsychology of hemispherectomy can be used to inform education theory makes for an intriguing and readable book—part case history, part speculation, and from time to time—part educational manifesto. Throughout, however Battro manages to communicate the intricacies of brain surgery, neuronal architecture, developmental psychology, and functional imaging in such a way as to render the take-home message for "an epigenetic neurocognitive approach" both relevant and understandable. Supporting his own position that in such cases half brain amounts to is a "new brain", Battro makes full use of the power of detailed single case observations to illustrate how Nico's abilities (musical motor and attention) have all developed normally despite the traditional belief that these functions were mediated by the right hemisphere. The only major behavioural impairment that Nico retained was poor constructional and handwriting skills, a handicap that Battro successfully succeeds in compensating by providing a computerised "information prosthesis".

Although some may take issue with some of the generalisiations and speculations offered—overall the book revisits important issues relevant to neuropsychology that deserve consideration by clinicians and neuroscientists alike.

PETER HALLIGAN

Neurobehavioural disability and social handicap following traumatic brain injury. Edited by RODGER LL WOOD and TOM M MCMILLAN (Pp 315, £39.95). Published by Psychology Press, Hove, 200. ISBN 0 863 77889 5.

This book is one of a series entitled *Brain damage, behaviour and cognition*. It comprises 13 chapters in three parts. The first part covers "the nature and impact of neurobehavioural disability"; the second addresses "rehabilitating neurobehavioural disability" and the final part is concerned with "models of service delivery". Although the contributors come from the United Kingdom, North America, and Australia, the focus (to a large extent) is on British rehabilitation.

To my mind the best section, overall, was part three, "models of service delivery". I found chapter 12 by McMillan and Oddy "service provision for social disability and handicap after acquired brain injury" helpful and informative and full of common sense. The previous chapter by Giles "the effectiveness of neurorehabilitation" was also useful, not least because of the many outcome studies referred to. Of the treatment chapters, chapter 8 by Alderman and chapter 9 by Evans on "challenging behaviours" and "the dysexecutive syndrome" are well worth reading. Parts of the book came over as either rather bland or less useful for readers of this *Journal*.

The main take home message is captured in chapter 12—namely that "Brain injury rehabilitation is best conducted in services dedicated to those with acquired brain injury, for the majority of whom personality changes and cognitive impairments are the primary disabilities". Given firstly, the low priority of rehabilitation for people with cognitive and personality changes after acquired brain injury; secondly, the fact that many with traumatic brain injury are sent to any ward that has an empty bed; and thirdly, that many are under the care of orthopaedic surgeons or rheumatologists rather than specialists in brain injury, it is to be hoped that neurologists, neurosurgeons, psychiatrists, and health service providers will pay heed to this message.

BARBARA A WILSON

Benign childhood partial seizures and related epileptic syndromes. By C P PANAYIOTOPOULOS (Pp 406, £60.00). Published by John Libbey, London, 1999. ISBN 086196 577 9.

This book is the result of the author's long standing interest in and contributions to benign epilepsies, particularly those of occipital origin. It is a tremendously useful source book for both the literature and clinical examples of this group of disorders and more than half of the chapters are devoted to the occipital epilepsies.

Dr Panayiotopoulos puts forward the view that the benign childhood partial seizure disorders should be regarded as one common genetically determined functional derangement but the case for this except in the broad phenotypic classification sense is not made. He thinks that his proposed name of benign childhood (occipital centrotemporal, frontal) seizure susceptibility syndrome has not been taken up in the way in which he would have liked. Some early parts of the book on how to manage a neurophysiology department are not strictly relevant to the main purpose.

The historical insights into these conditions are fascinating and Dr Panayiotopoulos is to be congratulated on providing a tremendously valuable analysis of this huge literature, which will be used by those working with the developmental epilepsies.

BRIAN GR NEVILLE

Quality of life in epilepsy: beyond seizure counts in assessment and treatment. Edited by GUS A BAKER and ANN JACOBY. (Pp 316, £38.00). Published by Harwood Academic Publishers, Amsterdam, 2000. ISBN 90 5823 121 6.

The issue of quality of life in epilepsy has developed enormously over the past 10 years. Although this is still rather belated in relation to other conditions where the issue has been around for much longer, there is a healthy debate ongoing about what indeed is quality of life and it is likely that no answer to this question will ever be forthcoming. Nevertheless, in terms of health outcome research, there is a place for quality of life measurement.

Epilepsy, perhaps more than many other medical disorder, is associated with profound deleterious psychological and sociological consequences that are not always directly related to the actual disease process. Instead, severe disability results from the fear that an epileptic seizure might occur at some time in the future and from the negative public image associated with the diagnosis itself. People with epilepsy, who may be perfectly normal apart from the fact that epileptic seizures occur or might occur from time to time, are commonly subjected to limitations on their daily activities ostensibly to protect them or others from injury or even death. Seizures can occur without warning, which fosters a sense of insecurity that affects social development. Opportunities for satisfying interpersonal relationships are further compromised when seizures begin in childhood and parents adopt an overprotective attitude that prevents the acquisition of skills required for a full independent life. All these introduce disabilities, which potentially threaten the quality of life of people with epilepsy.

In the past decade, instruments to measure quantitatively the health related quality of life in epilepsy have been developed. Consequently, today in most major epilepsy centres, effectiveness of treatment is no longer measured only by frequency of seizures. The impact that treatment has had on the patients' perception of improvement and their predicament and vital capacity to live independent fulfilling lives are important considerations.

This book, edited by two of the leading workers in this field, is a good review of what is going on in the field of measurement of quality of life. It is comprehensive, encompassing almost every aspect of this domain. An excellent review of currently available quality of life measures is one of the highlights of the book. Chapters covering quality of life issues for children, adolescents, and older people with epilepsy as well as people with learning disabilities and epilepsy are also present. This book would no doubt enhance the library of any person with an interest in measuring outcome in epilepsy.

LEY SANDER

CORRECTION

Johnson MR, Sander JWAS. The clinical impact of epilepsy genetics. *J Neurol Neurosurg Psychiatry* 2001;**70**:428-30.

In paragraph 2, left column, p 428, the word "idiopathic was misplaced during the editorial process. The paragraph should read: "The role of inheritance in epilepsy is traditionally categorised according to the mechanism of inheritance: (1) mendelian disorders in which the epilepsy forms part of the phenotype; (2) idiopathic epilepsies with mendelian inheritance; (3) idiopathic epilepsies with complex inheritance; (4) epilepsies associated with cytogenetic abnormality."